## Remarks

Applicants appreciate the Examiner's acknowledgement in the Advisory Action mailed April 26, 2007, that claims 1 and 23, as originally filed in parent application 09/433,486, provide support for the limitation "0.5 $m^2$/ml" in claim 16 as pending.

## Rejection Under 35 U.S.C. § 103

Claims 16-21 and 34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Application Publication No. 2001/0018072 to Unger ("Unger"). Applicants respectfully traverse this rejection.

*Legal Standard*

When applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to:

(a) determining the scope and contents of the prior art;

(b) ascertaining the differences between the prior art and the claims in issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating evidence of secondary considerations.

*Graham v. John Deere*, 383 US 1, 17-18, 148 U.S.P.Q. 459, 467 (1966). These four factors are traditionally referred to as the Graham factors.

The Graham factors were recently affirmed by the U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). In its analysis of the obviousness standard, the Court did not totally reject the Federal Circuit's prior use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis.

Rather, the Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter may provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

The Court also warned against the use of hindsight analysis in making an obviousness determination. The Court stated, "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR*, 127 S. Ct. at 1742, citing *Graham*, 383 U.S. at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412, 141 U.S.P.Q. 549 (6th Cir. 1964))).

In response to the *KSR* decision, the Deputy Commissioner for the USPTO issued a memorandum stating: "[I]n formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Memorandum from Margaret A. Forcarino to Technology Center Directors (May 3, 2007).

Analysis

As discussed above, the United States Supreme Court in *KSR* reaffirmed the *Graham* factors an obviousness analysis. The *Graham* factors are analyzed below:

***(a) Determining the scope and contents of the prior art***

The scope and contents of the prior art must be made *at the time the invention was made*. The requirement "at the time the invention was made" is to avoid impermissible

hindsight. "It is difficult but necessary that the decision maker forget what he or she has been taught [...] about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983).

Unger describes a solid porous matrix containing a surfactant in combination with a bioactive agent (page 1, paragraph 0013). The matrix may be prepared by (1) combining a surfactant and a therapeutic, together with a solvent, to form an emulsion containing random aggregates of the surfactant and the therapeutic, and (2) processing the emulsion by controlled drying, or controlled agitation and controlled drying to form the solid porous matrix (abstract and page 1, paragraph 0014).

Unger is concerned with the targeted delivery of therapeutics to a particular region of patient (page 1, paragraph 0002). The compositions described in Unger may contain a stabilizing material, which is capable of improving the stability of the vesicles (e.g., liposomes, lipospheres, particles, etc.) containing gases, gaseous precursors, steroid prodrugs, targeting ligands, and/or other bioactive agents (page 2, paragraph 0031). The stabilizing material can be used to prevent the escape of gases, gaseous precursors, steroid prodrugs, targeting ligands, and/or other bioactive agents.

***(b) Ascertaining the differences between the prior art and the claims***

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious.

*Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983).

***The Claimed method***

The claims define a method for making porous drug matrices. As discussed in the specification, such drug matrices are particularly useful for increasing the dissolution rates for drugs, especially drugs with low aqueous solubility (*see* page 2, lines 23-27). The matrices contain at least one excipient which enhances the dissolution rate of the drug, stabilizes the drug in an amorphous form by preventing crystallization, and/or stabilizes the drug in crystalline form by inhibiting crystal growth.

Independent claim 16 and its dependent claims, claims 17-21, define methods for making a pharmaceutical composition that contains a porous matrix formed of at least one hydrophilic or hydrophobic excipient and microparticles of a drug. As specified in claim 16, the method requires the following steps:

(a) dissolving a drug in a volatile solvent to form a drug solution,

(b) combining at least one volatile solid pore forming agent with the drug solution to form an emulsion, suspension, or second solution,

(c) incorporating at least one excipient into the emulsion, suspension, or second solution, wherein the excipient is selected from the group consisting of hydrophobic and hydrophilic excipients which enhance dissolution rate, which stabilize drug in amorphous form by preventing crystallization, and which stabilize drug in crystalline form by inhibiting crystal growth, and

(d) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug and excipient.

Independent claim 16 also specifies physical properties of the composition produced by this method. The resulting composition contains microparticles of drug that have a mean diameter between about 0.1 and 5 μm and a total surface area greater than about 0.5 $m^2$/mL. Additionally the composition contains a dry porous matrix in a dry powder form, which has a TAP density of less than or equal to 1.0 g/mL and a total surface area of greater than or equal to 0.2 $m^2$/g.

As discussed in detail below, Unger describes a different method and different compositions are produced using Unger's method.

**Unger does not disclose or suggest elements (b), (c), and (d) of claim 16**

***Unger does not disclose or suggest adding a volatile solid pore forming agent to the drug solution and then removing the volatile solid pore forming agent***

Unger describes the use of gases or gaseous precursors, which are **entrapped** within the matrix (page 20, paragraph 0160 to page 22, paragraph 0175). Unger alleges that the entrapped gas provides the solid porous matrix with enhanced reflectivity. The gas and/or gaseous precursors are not "pore forming agents" nor are they removed from the matrix. Unger also describes the use of gaseous precursors as a solvent in the preparation of the solid matrix (page 20, paragraph 0161). Solvents, by definition, are generally liquids. In contrast, the claimed method requires the addition of a volatile **solid** pore forming agent, which is removed and upon removal, forms a porous matrix.

While Unger discloses that the gaseous precursor may be added to the surfactant and the therapeutic and removed during processing (page 20, paragraph 0161), this

disclosure is specifically in regard to gaseous precursors that are used as **solvent** in the preparation of a solid porous matrix. None of the examples describe adding a volatile solid pore forming agent to a drug solution to form a suspension, emulsion, or second solution and then removing the volatile solid pore forming agent to form a porous matrix.

In the Advisory Action mailed April 26, 2007, the Examiner stated "…Unger teaches the steps of dissolving the drug in a volatile organic solvent in the presence of pore forming agents, such as bicarbonate of PEG, lyophilizes or vacuum dries or spray dries the suspension or emulsion to form the porous matrix is described in paragraphs 0184-0190". This statement mischaracterizes Unger's disclosure.

First, there is no reference to bicarbonate of PEG anywhere in Unger.

Second, paragraphs 0184-190 cited by the Examiner do not disclose or suggest the use a volatile **solid** pore forming agent to form a porous matrix. Paragraph 0184 discloses that a solid porous matrix containing a surfactant and a therapeutic is prepared by combining a solvent, a surfactant, and a therapeutic to form an emulsion in the form of a random aggregate. In the case of spray drying, the emulsion or colloidal suspension is placed into association with a blowing agent, such as methylene chloride. Methylene chloride is a volatile organic **solvent**; it is not a volatile **solid** pore forming agent as required by the claims.

***Unger's Example 1 does not meet the limitations of Claim 16***

In the Final Office Action mailed December 8, 2006, the Examiner alleges that prophetic Example 1 in Unger describes steps (a), (b), and (d) of claim 16. This allegation is incorrect. Example 1 describes the encapsulation of dexamethasone in PEG Telomer B, which is a surfactant. Unger predicts that 20% of the PEG-Telomer B

aggregate complex is dexamethasone. PEG Telomer B is not a volatile pore forming agent. PEG Telomer B is not removed from the mixture. Further, even if one could argue that PEG Telomer B is a volatile pore forming agent, it is not a volatile **solid** pore forming agent. PEG Telomer B is a liquid having a boiling point of 200°C (*see* the Material Safety Data Sheet for PEG Telomer B, a copy of which is enclosed). Example 1 does not disclose the addition of a volatile solid pore forming agent to a drug solution. Further, Example 1 does not disclose removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug and excipient as required by claim 16.

***Volatile Solid Pore Forming Agents are a subset of Pore Forming Agents***

Claim 16 requires a **volatile** solid pore forming agent. "Volatile" agents are agents that change readily from a solid or liquid to a vapor (*see* the enclosed definition from www.wordnet.princeton.edu). The compounds are typically evaporated using added heat and/or vacuum (page 20, lines 22-24 of the specification).

The references cited by the Examiner in the Final Office Action mailed December 8, 2006 disclose agents that form pores by dissipating out of the composition *in situ* into the surrounding tissues or bodily fluids; they are not volatilized during formation of the porous matrix as required by the claims. Sodium chloride has a melting point of 800°C and a boiling point of 1,465°C (*see* the Material Safety Data Sheet for salt, a copy of which is enclosed). Starch decomposes at 250°C, which is before its melting point (*see* the Material Safety Data Sheet for starch, a copy of which is enclosed). Thus, these materials do not evaporate readily at relatively low temperatures and pressures; i.e., they

are **not** volatile. Further, the pore forming agents required by the pending claims are removed during processing, i.e. prior to introducing the composition into the body; not *in situ* as required by the references cited by the Examiner. Contrary to the Examiner's assertion, any agent that is listed in any prior art reference as a "pore forming agent" does not necessarily meet the limitations of claim 16.

***Unger does not disclose compositions containing an excipient which enhances the dissolution rate of the drug, stabilizes the drug in an amorphous form by preventing crystallization, and/or stabilizes the drug in crystalline form by inhibiting crystal growth***

As discussed above, Unger discloses the use of a stabilizing material. Unger's stabilizing material is used to stabilize the vesicle containing the active agent and/or to prevent escape of the gases, gaseous precursors, and/or bioactive agents. Unger does not disclose or suggest the use of at least one excipient which enhances the dissolution rate of the drug, stabilizes the drug in an amorphous form by preventing crystallization, and/or stabilizes the drug in crystalline form by inhibiting crystal growth.

**Unger does not disclose or suggest microparticles with the properties required by claim 16**

Claim 16 specifies the properties of the compositions formed using the claimed method. Unger does not disclose or suggest that the microparticles formed using its process have the properties specified by claim 16.

***(c) Resolving the level of ordinary skill in the art***

One of ordinary skill in the art at the earliest priority date would likely have a master's degree in chemistry, chemical engineering, or pharmaceutics with

approximately five years experience or a Ph.D. in chemistry, chemical engineering, or pharmaceutics with approximately three years experience.

***(d) Evaluating evidence of secondary considerations***

Secondary considerations to be considered include commercial success, long felt but unresolved needs, failure of others, etc.

The claims are drawn to methods of making pharmaceutical compositions. These methods are particularly useful for formulation pharmaceutical compositions containing drugs having low solubility. As discussed in the specification, the bioavailability of a drug can be limited by poor dissolution of the drug into aqueous bodily fluids following administration (page 1, lines 17-18). This rate- limiting step can be critical to rapidly attaining therapeutically effective drug levels (page 1, lines 18-20).

Traditional approaches to parenteral delivery of poorly soluble drugs include using large volumes of aqueous diluents, solubilizing agents, detergents, non-aqueous solvents, or non-physiological pH solutions (page 1, lines 20-23). These formulations, however, can increase the systemic toxicity of the drug composition or damage tissues the site of administration (page 1, lines 23-25).

Other approaches disclosed in the prior art have focused on the physical form of the drug itself. For example, drugs have been prepared in nanoparticulate form. Nanoparticles, however, can be difficult to produce and maintain in a stable form due to their tendency to flocculate or agglomerate, particularly in the absence of surface modifying agents absorbed or coated onto the particles (page 1, line 31 to page 2, line 3). Further, techniques used for nanonization are typically undesirable due to: (1) the time it takes to process a single batch (e.g., several days); (2) scale up of such techniques can be

difficult and costly; and (3) the process can be difficult to conduct aseptically (page 2, lines 3-8). Thus, at the time of the priority application, there existed an unmet need for formulations containing poorly soluble drugs which exhibit increased dissolution of the drug. The claimed methods are quite versatile and can be used with drugs having varying solubilities to increase the dissolution rate.

Application of the Graham factors demonstrates that one or ordinary skill in the art would not have been motivated to modify Unger to arrive at the claimed methods. Unger is concerned with targeted drug delivery, not formulating poorly soluble drugs to have enhanced dissolution *in vivo*. Unger describes the use of stabilizing materials to stabilize the vesicle containing the active agent, not to enhance dissolution or prevent crystallization of the drug as required by claim 16. Unger does not disclose or suggest steps (b), (c), and (d) of claim 16. Unger does not disclose or suggest microparticles having the properties defined in claim 16. One of ordinary skill in the art would not be motivated to modify Unger to arrive at the claimed methods. Therefore claims 16-21 are not obvious in view of Unger.

Allowance of claims 16-21 and 34 is respectfully solicited.

Respectfully submitted,

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